

Application No. 10/006,593

Docket No.: ALEX-P01-054

**REMARKS**

Claims 1-3, 5-11, 18-23, 36, 44, 85-87, 89, and 96-126 constitute the pending claims in the present application.

**Claim Rejections Under 35 U.S.C. §103**

Claims 1-3, 5-11, 18-19, 22-23, 36, 96, 99, 100-101, 104-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (a) in view of Dower et al. and Barbas et al. (b) in view of Cwirla et al. and further in view of Wrighton et al. as evidenced by Helms.

Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein an agonist peptide (such as an EPO or TPO mimetic) replaces a single portion of a complementarity determining region and wherein the immunoglobulin molecule or fragment thereof binds to and agonizes a receptor (such as an EPO or TPO receptor) as claimed in the instant application.

The Examiner appears to be rejecting the claims based on some teaching, suggestion, or motivation to combine prior art references. The guidelines with regard to this standard are set forth in Rationale G in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 (see Federal Register, Volume 72, No. 195, pages 57526-57535 (October 10, 2007)):

G. Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention;

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

As noted in Applicants' previous responses, Barbas et al. (a) discloses inserting peptides into CDR regions to generate antagonists (see e.g., page 75, lines 29-34, and pages 78-83). Barbas (b) discloses autoantibodies that bind to DNA. Such antibodies do not even bind to a receptor let alone

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suggest that such antibodies could be used to *agonize* receptor activity. Possibly the Examiner meant to cite to a different publication, this being Barbas et al., *Proc. Natl. Acad. Sci. USA* 88:7978-7982 (1991). The Examiner suggests that a person skilled in the art would have been motivated and had a reasonable expectation of success by combining the CDR replacement strategy of Barbas et al. (a) with the peptides of Cwirla and Wrighton. Applicants strenuously disagree.

"[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Examination Guidelines for Determining Obviousness under 35 U.S.C. 103, citing *KSR International Co. v. Teleflex, Inc.*, 550 U.S. \_\_\_, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

As noted in Applicants' response of April 19, 2007, nothing in the cited references or in the general knowledge teaches the combination of Cwirla, Wrighton, or Helms with either Barbas reference. Cwirla and Wrighton are directed to the discovery of *small peptides* that can be used as agonists of the EPO or TPO receptor. In particular, both references utilize a phage display library to isolate peptides that *bind* to the desired receptor. These peptides are then synthesized as *isolated peptides* and tested for receptor agonist activity. In particular, Wrighton notes that "[t]his discovery may form the basis for the design of *small molecule* mimetics of EPO" (see abstract; emphasis added) and that "[s]*mall molecule* EPO mimetics may have desirable pharmacological properties such as oral bioavailability or the ability to be delivered trans-dermally" (see page 463, emphasis added). The Examiner alleges that one of ordinary skill would be motivated to combine the references because it is well known that peptides generally have short serum half-lives (see page 7). This would be doing exactly the opposite of the teachings of Wrighton. The mimetics of Wrighton were developed for particular pharmacological properties, such as oral bioavailability; those properties would likely be destroyed by incorporating the peptides into immunoglobulins.

Applicants request clarification from the Examiner regarding rejections citing the Helms et al. reference. The Examiner rejects claims 1-3, 5-11, 18-19, 22-23, 36, 96, 99-101, and 104-126 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (a) in view of Dower et al. and Barbas et al. (b) in view of Cwirla et al. and further in view of Wrighton et al. as evidenced by Helms. However, on page 7 the Examiner appears to be rejecting only the claims wherein at least one flanking sequence is included (in particular claims 2 and 3) using Helms et al. Claim 2 is

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directed to a TPO receptor agonist comprising an immunoglobulin, wherein a portion of a CDR is replaced with a TPO mimetic and wherein at least one amino acid is covalently linked to at least one end of the mimetic.

The Examiner admits that Helms teaches that the introduction of novel sequences into CDRs can significantly diminish the stability of immunoglobulins. The Examiner alleges that Helms also discloses introducing flanking sequences covalently linked to the introduced CDR sequences. Nothing in the cited references or the general knowledge of one of ordinary skill would lead to a combination of Helms with any of the other cited references. The Barbas references are silent with regard to the stability of the immunoglobulins and in fact the immunoglobulins work for their intended purpose as antagonists. A person skilled in the art lacks any motivation to modify functional antagonists with flanking sequences from a reference that teaches the instability of its immunoglobulins. The Examiner has thus failed to demonstrate a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Additionally, the Examiner has failed to demonstrate a finding that there was a reasonable expectation of success. The Examiner is required to articulate why a person skilled in the art would expect that a CDR replacement strategy that produces antagonists would result in EPO and TPO agonists.

The Examiner states that "the functions of the antibodies produced by the method of Barbas (a) are irrelevant" (see page 6). The functions of the antibodies of the prior art are in fact quite relevant in the examination of obviousness. The Examiner states further on page 7 that an ordinary skilled person would have had a reasonable expectation of success to increase the half-life of an agonist peptide by grafting into a human antibody framework CDRs. The relevant question, however, is whether an ordinary person would have had a reasonable expectation of success of producing functional agonists by grafting a peptide into a human antibody framework CDR. The Examiner provides no support that an ordinary person of skill would have expected to produce agonists using a method that previously produced only antagonists.

In fact, as evidenced by the Declaration of James D. Marks, submitted herewith, a person of ordinary skill at the time of the invention would not have had an expectation of success of

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generating receptor agonists using a CDR replacement strategy that produces antagonists. As explained in the Declaration, agonists and antagonists mediate their functions by vastly different molecular mechanisms. An antagonist is only required to interfere with the binding of a receptor and its corresponding ligand, while an agonist must induce a conformational change in the receptor that transduces into an activation signal. The Declaration further explains that because of the specific conformation requirements required for activating a receptor, a person skilled in the art would not expect that the Cwirla and Wrighton peptides could be inserted into CDR regions and maintain their ability to 1) bind receptor, 2) dimerize receptor, and 3) activate receptor by providing the proper conformation of receptor assembly. Based on the knowledge of receptor activation and the teachings of Barbas, a skilled person would actually expect that insertion of peptides into a protein scaffold would likely interfere with the conformation of peptide-receptor binding and prevent receptor activation or could even result in formation of a receptor antagonist. Accordingly, the Examiner has clearly failed to demonstrate that one skilled in the art would have had a reasonable expectation of producing an agonist molecule comprising a peptide incorporated into a CDR of an immunoglobulin based on the teachings of the cited references.

Alternatively, the Examiner may be attempting to reject the claims as "obvious to try". The guidelines with regard to the "obvious to try" standard are set forth in Rationale E in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103:

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The present claims relate to TPO and EPO receptor agonists comprising peptide mimetics inserted into CDR regions. At the time of the invention, the CDR replacement strategy of Barbas

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was not one of the known predictable solutions of generating agonists with increased in vivo half-life. Applicants were the first to demonstrate that this strategy would work for generating agonists. Furthermore, as previously noted, the Examiner has failed to demonstrate that one of ordinary skill would have a reasonable expectation of success in generating agonists using a strategy shown to produce antagonists.

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-11, 18-19, 22-23, 36, 44, 85-87, 89, and 96-126 were rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the specification does not enable an immunoglobulin or antigen fragment thereof comprising a CDR wherein a TPO mimetic replaces a single portion of said CDR. Applicants respectfully disagree.

The Examiner's attention is drawn to Example 7 in the specification which describes the construction of a heavy chain CDR2 library. CDR2 is partially replaced by the TPO mimetic peptide. The first 10 amino acids of CDR2 were replaced with 11 amino acids of TPO mimetic peptide and flanking sequence while 7 amino acids of CDR2 remain. The library was subsequently panned for binding to cMpl-R. The specification, therefore, provides a working example of an immunoglobulin wherein a portion of a CDR is replaced with a peptide mimetic.

Furthermore, Applicants respectfully disagree with the Examiner's reliance on the Rudikoff et al., Colman et al. and Ibragimova references. The Examiner points to the references to demonstrate that even minor changes within the CDR sequences are known to dramatically affect the binding function of an antibody. As Applicants have explained in our previous response (mailed April 19, 2007), the binding ability of the claimed immunoglobulin molecules does not depend on the precise three dimensional conformation of the CDR regions as is the case for conventional antibody-antigen interactions. The peptide mimetics are inserted into the CDRs only because these regions are solvent exposed. As opposed to a typical antibody wherein it is necessary for the six different CDRs to be in the proper conformation relative to each other for proper binding to the antibody target and where a change in the antibody sequence may disrupt the normal conformation, in the present case the immunoglobulin is acting as a carrier for a peptide and it is merely necessary for the peptide mimetic within the carrier to be exposed and to retain its activity, the remaining 5 CDRs are irrelevant. There is no need for six separate CDRs to bind a single target in the claimed

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molecules, rather only the mimetic needs to bind the target. The CDR sequence that is being replaced by the mimetic is irrelevant to the activity of the mimetic.

The Examples provided in the application clearly demonstrate that the immunoglobulin is acting as a carrier for a peptide rather than acting as a conventional antibody. In particular, Example 1 involves grafting of a TPO mimetic into the HCDR3 region of an anti-tetanus toxoid (anti-TT) Fab. The original anti-TT Fab and several anti-TT Fabs having a TPO mimetic inserted into the HCDR3 region were tested for binding to the original antigen. The specification shows that the anti-TT Fab bound to its antigen TT but did not bind to BSA (e.g., the binding of the unmodified anti-TT Fab was specific for its antigen). However, the four TPO-mimetic peptide grafted clones did not show significant binding to TT or BSA. (See page 43, lines 17-22 of the instant application.) In addition, anti-TT Fabs containing a TPO mimetic inserted into the HCDR3 region demonstrated strong binding to cells transfected with cMpl-R, the TPO receptor, but did not bind to control cells not expressing cMpl-R. The original anti-TT Fab does not bind to control cells or cells transfected with cMpl-R. (See page 44, lines 8-14 of the instant application.) Therefore, replacement of anti-TT Fab HCDR3 with a TPO mimetic was sufficient to change the binding specificity of the Fab. Furthermore, the specification clearly demonstrates that the anti-TT Fabs containing a TPO mimetic in the HCDR3 region could bind to the TPO receptor and activate the receptor. (See e.g., Example 1 starting at page 40, especially the section labeled "Biological Assays" on page 46, line 3 through the Table on page 47.) Accordingly, the specification clearly demonstrates that the immunoglobulin referred to in the instant claims is acting as a carrier rather than a conventional antibody and therefore clearly enables the claimed molecules.

The working examples further demonstrate that the peptide mimetics may be inserted in HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 and in each case result in immunoglobulins that act as agonists. This is in sharp contrast to conventional antibodies where amino acid sequences cannot be swapped between CDR regions. Further, the lengths of the peptide mimetics are not necessarily the same as the CDRs which they replace. For example, Examples 2 and 3 teach the replacement of HCDR2 or HCDR3 together with LCDR1, LCDR2 or LCDR3. The TPO mimetic being inserted is 14 amino acids and flanking regions are also included. The CDR lengths being replaced are: HCDR2 is 17 amino acids, HCDR3 is 16 amino acids, LCDR1 is 12 amino acids, LCDR2 is 7 amino acids, and LCDR3 is 8 amino acids. This demonstrates that there is not a strict

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size limitation on the mimetic being inserted. The results of the working examples demonstrate that the claimed immunoglobulins are not subject to the same structural requirements as conventional antibodies. As noted previously, this is due to a different mechanism of binding the desired target. Therefore, the Examiner is incorrect when he states that the structural integrity of the CDRs is important for the functionality of such immunoglobulin molecule. The presently claimed immunoglobulin molecules are merely carriers for peptide mimetics that are inserted into solvent exposed CDRs; they are not meant to act as conventional immunoglobulins, but rather as agonists.

The Examiner states on page 9 of the Office Action that the specification "does not enable immunoglobulin or antigen fragment thereof wherein one or more amino acid residues of each of two CDRs are replaced with a peptide mimetic". Replacement of "each of two CDRs" is not a feature of the pending claims, however. Applicant believes this rejection to be improper and requests clarification from the Examiner.

The Examiner further notes that the specification is completely silent in regard to the substitution of HCDR1. In fact, replacement of HCDR1 with a peptide is specifically described on page 3, lines 18-19. The application also sets forth working examples showing that agonist peptide mimetics can be inserted into HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 and it would seem reasonable to believe that inserting the peptide mimetic into HCDR1 would also work, since all that is required is for the peptide mimetic to be solvent exposed. If the Examiner intends to make a rejection, he is required to set forth a prima facie case, i.e., he needs to state one or more reasons as to why he would doubt that a peptide mimetic inserted in HCDR1 would fail to retain agonist activity. The lack of a specific working example is not by itself a reason to reject a claim. Applicants assert that no prima facie case has been set forth.

The Examiner further alleges that the skilled person would need to perform undue experimentation in order to practice the claimed invention. Applicants respectfully disagree. The disclosure provides working examples for replacing HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 with a peptide mimetic. The disclosure also provides in Example 7 the partial replacement of a CDR. CDRs are of a limited length from 5 to 17 amino acids. Replacement of one or more amino acid residues would be routine and easily tested. The specification sets forth the idea of inserting peptide mimetics into immunoglobulins to generate agonists. The specification further provides sufficient guidance and working examples to enable one of ordinary skill in the art to

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practice the invention over the scope of the claims without undue experimentation. This includes disclosure concerning methods of making and screening phage libraries in which large numbers of antibody constructs can be easily screened.

In setting forth the argument that the claims are not enabled and that undue experimentation would be required, the Office Action cites several publications. The first of these is Rudikoff et al. which teaches that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. The Office Action specifically mentions the case wherein the change of a single amino acid in a CDR of a myeloma protein resulted in the loss of antigen-binding. This is irrelevant. What Rudikoff teaches are antibodies that bind to specific antigens. This binding specificity is determined by the 6 CDRs. Changing the sequence of a CDR would not surprisingly interfere with the ability of the antibody to properly bind its target antigen. It is after all those amino acids in the CDRs that need to interact with the target antigen. In the present application it must be noted that the peptide mimetics being inserted into the CDR regions always retain their complete sequence, i.e., *no changes are being made to the peptide mimetic sequence itself*. Therefore there is no reason to assume that the peptide mimetic will lose its activity. The Colman publication mostly does not discuss its findings in terms of CDRs or frameworks, but it does seem to be discussing amino acid substitution in "antibody-antigen interfaces". Again, it is the CDRs which tend to directly contact the target and thus will be at the antibody-antigen interface and as already noted, changes in CDRs themselves can be expected to affect binding. But to repeat the point above, the inserted peptide mimetics are being inserted without any changes to the mimetics and thus there is no reason to believe that they will lose their mimetic activity. Concerning the Ibragimova and Wade publication, Applicants do not disagree that small changes may affect the folding of a protein. But as previously discussed, whereas an antibody acting as a normal antibody is required to properly fold such that 6 separate CDRs will all appropriately contact the antigen, in the case of the agonist being claimed one is concerned only with a single short region and there is no need for exquisitely proper folding to enable 6 separate regions to be in their proper 3-dimensional positions; rather one needs only to have the single peptide in a position such that it is exposed and can interact with its target receptor. Thus the mimetic should be able to tolerate a lot of change to the overall structure of the antibody

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without losing its agonist activity. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 1-3, 5-8, 18, 22, 23, 36, 44, 85, and 97-112 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 11, 16, 26-35, and 38-56 of copending Application No. 10/307,724. Applicants note that they will address the rejection, if appropriate, upon indication of allowable subject matter. Applicants respectfully request that the Examiner hold the rejection in abeyance until the appropriate time.

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CONCLUSIONS

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due other than those itemized on the enclosed transmittal. However, should an additional fee be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, from which the undersigned is authorized to draw under ALEX-P01-054.

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Respectfully submitted,

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